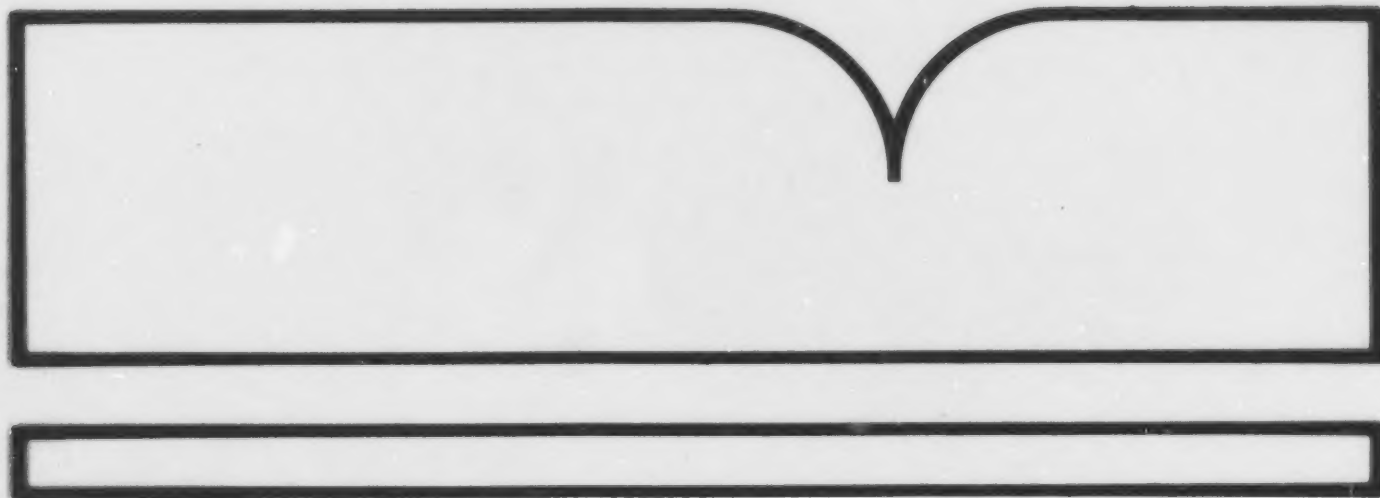


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Hazard Associated with Exposure to
Carcinogens and Other Toxic Chemicals

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METHODOLOGY FOR RANKING THE DEGREE OF HAZARD
ASSOCIATED WITH EXPOSURE TO
CARCINOGENS AND OTHER TOXIC CHEMICALS

by

Elizabeth L. Anderson^a, Margaret Chu^b,

Michael Dourson^c, and Christopher DeRosa^c

^aDirector, Office of Health and Environmental Assessment
U.S. Environmental Protection Agency
Washington, DC 20460

^bToxicologist, Carcinogen Assessment Group
Office of Health and Environmental Assessment

^cEnvironmental Criteria and Assessment Office
Office of Health and Environmental Assessment Office
Cincinnati, OH 45268

OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT
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16. ABSTRACT A hazard index is an overall indicator of the potential harm of a hazardous substance to humans and the environment. This paper describes the use of a carcinogenicity index and a systemic (chronic) toxicity index in setting reportable quantities under Section 101(14) of the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) of 1980. The three types of evidence used to evaluate a substance's carcinogenic hazard are 1) epidemiological, 2) experimental and 3) supportive evidence from short-term tests, metabolism and pharmacokinetics and structure-activity correlations. Hazardous substances suspected of carcinogenic potential are ranked by the level of this evidence and the potency factor. The potency factor is $1/ED_{10}$, where ED_{10} is the estimated dose associated with a lifetime cancer risk of 10%. The toxicity index for substances with systemic (chronic) toxicity potential is based on the minimum effective dose levels for chronic exposures via environmental media and the type of effect. About 200 potential carcinogens and 200 chemicals associated with other diseases have been evaluated and assigned a hazard ranking.		
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Elizabeth L. Anderson^b, Margaret Chu^c,
Michael Dourson^d, and Christopher DeRosae^e

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^bDirector, Office of Health and Environmental Assessment, RD-689, U.S. Environmental Protection Agency, 401 M St., S.W., Washington, D.C., 20460.

^cToxicologist, Carcinogen Assessment Group, Office of Health and Environmental Assessment.

^dToxicologist, Environmental Criteria and Assessment Office - Cincinnati, Office of Health and Environmental Assessment.

^eEcologist, Environmental Criteria and Assessment Office - Cincinnati, Office of Health and Environmental Assessment.

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I. INTRODUCTION

Inadvertent exposures of populations to hazardous chemicals make it necessary for public health officials to have immediate knowledge of the severity of potential effects and the doses that cause the effects observed. A hazard index has been developed in response to the need to establish a rating scheme to characterize hazardous chemicals according to the severity of disease and the associated hazards, and to prescribe quantities of hazardous chemicals which, when spilled, must be reported to the U.S. Environmental Protection Agency. About 200 potential carcinogens and 200 chemicals associated with other diseases have been evaluated. The hazard index for potential carcinogens couples the weight of evidence indicating potential carcinogenicity with the potency of the chemical to rate the relative cancer hazard. Similarly, the hazard index for chemicals that may cause other diseases couples rating factors for the severity of disease with the dose which causes the onset of disease to rate the relative hazards of these chemicals. These hazard indexes and the data for the chemicals thus far evaluated may have more general applications in assessing chemical risks to the public in response to accidental exposures.

Toxicity indexes, such as lethal dose for 50% of animals (LD₅₀) and no-observed-effect-level (NOEL) can be used in the setting of permissible levels of harmful substances in the environment or for setting priorities of concern of harm to human health or the environment. Hazard index can be defined as the overall indicator of potential harm of a hazardous substance to humans and the environment. Hazard indexes can be estimated by taking into consideration all parameters related to the fate, effects, and dose-response characteristics of the hazardous substances. Thus the chemical structure; physicochemical properties; mechanisms of action; chemical, biological and environmental transformation and

transport; and toxicity indexes are important parameters for estimating hazard indexes of chemicals in the environment.

Some of the above parameters can be estimated from experimental data, while others may have to be estimated using statistical techniques. The extent and the form of hazard indexes depends on the purposes for which they are used.

This paper describes the use of a systemic (chronic) toxicity index and a carcinogenicity index in setting reportable quantities (RQ) under Section 101(14) of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA or "Superfund") of 1980. Section 103 of CERCLA requires immediate notification from any person in charge of a vessel or an offshore or onshore facility who releases an amount of a hazardous substance equal to or greater than its RQ. Under CERCLA Section 102(b), the RQ of any hazardous substance designated in Section 101(14) is one pound unless a different RQ has been established pursuant to Section 311(b)(4) of the Federal Water Pollution Control Act. These are statutory RQs for the CERCLA Section 101(14) hazardous substance unless and until the Administrator of EPA promulgates regulations establishing different quantities to be reported when released. CERCLA also permits EPA to establish a single RQ for each hazardous substance, regardless of the environmental medium into which the substance is released.

The Emergency Response Division of the Office of Emergency and Remedial Response proposed to use "Selected Criteria Processing" (SCP) to adjust the statutory RQs. SCP includes ignitability, reactivity, carcinogenicity, aquatic toxicity, acute mammalian toxicity (oral, dermal, inhalation) and chronic toxicity as the six primary criteria for adjusting RQs. The RQ for each hazardous substance is the lowest numerical value of all applicable RQs derived from the primary criteria. The RQ is then readjusted using biodegradability, hydrolysis, and photolysis as secondary criteria.

II. TOXICITY INDEX OF POTENTIALLY CARCINOGENIC SUBSTANCES

Hazardous substances suspected of carcinogenic potential are ranked using as toxicity index the level of evidence in support of their carcinogenicity and the strength (potency factor) they exhibit in inducing carcinogenic responses. Three types of evidence are used to evaluate a substance's carcinogenic hazard potential. They are: (1) epidemiologic evidence; (2) experimental evidence derived from long-term animal bioassays; (3) supportive or suggestive evidence from short-term tests, metabolism and pharmacokinetics, and structure-activity correlations.

THE WEIGHT-OF-EVIDENCE APPROACH TO EVALUATING THE EVIDENCE FOR CARCINOGENICITY

The weight-of-evidence is defined as the strength of evidence indicating potential carcinogenicity, not relative carcinogenic activity or potency of the agent. Thus, an overall decision as to whether an agent may pose a carcinogenic hazard to humans is based on a careful evaluation of all relevant scientific data, including the design and conduct of the study and the nature and type of responses. In the most complete form, a weight-of-evidence determination should be made from a consideration of the strengths and weaknesses of each piece of evidence, including epidemiological investigations, long-term animal studies, and supporting information.

Primary Sources of Information

Epidemiology Studies--

Human information provides direct evidence of the association of increases in tumor incidence or mortality in humans with exposure to chemicals. Well-designed and conducted analytical epidemiology studies, especially case-control and cohort investigations, are of prime importance; descriptive studies and case

reports provide ancillary information.

Important elements in interpreting the likely causality of epidemiological observations include the magnitude of the risk estimates (strength of the associations); the likelihood of their being due to chance (statistical significance); the rigor of the study design to avoid various kinds of bias, including those related to selection, confounding, classification, and measurement; the dose-response relationships; the temporal relationships between exposure and disease; the specificity of the associations; their biological plausibility; and the reproducibility of the findings.

Long-Term Animal Studies--

Confidence in the results of animal experiments is gained when carcinogenic effects have been confirmed in repeated experiments, in different animal strains or species, or in different dose groups or sexes within a given study. Other measures include demonstration of a highly significant increase in tumors, the presence of tumors at multiple anatomical sites, the histological types of tumors present, and the shortening of tumor latency in treated groups as compared with controls. Dose-response relationships also support a conclusion of carcinogenicity.

In reaching an overall evaluation of the experimental animal evidence, each long-term study is reviewed with regard to the following factors:

- a) tumor incidence
- b) tumor development
- c) preneoplastic lesions
- d) target-organ toxicity
- e) other relevant biological and chemical information.

Supportive Information

Short-Term Testing--

Appropriate in vivo and in vitro short-term tests provide ancillary empirical and potentially mechanistic information bearing on the carcinogenicity of an agent.

Biological Test Results--

Many toxicological, physiological, and biochemical observations, such as comparative metabolism and pharmacokinetic studies and certain mechanistic investigations, can contribute to a determination of carcinogenicity.

Structure-Activity Relationships--

General information bearing on the biological reactivity of compounds chemically related to the agent under investigation is useful in the evaluation of the carcinogenicity of the agent.

SUMMARIZING THE WEIGHT-OF-EVIDENCE FOR CARCINOGENICITY USING THE INTERNATIONAL AGENCY FOR RESEARCH ON CANCER (IARC) CRITERIA

After the data have been evaluated, the weight-of-evidence for carcinogenicity is classified according to the IARC criteria (see Appendix). In this approach the strength of the evidence for human and animal studies is evaluated separately, and all relevant factors are combined into an overall qualitative evaluation of the likelihood that the agent is a human carcinogen.

POTENCY FACTOR ESTIMATES

After the decision has been made that a compound has the potential for causing cancer in humans, a potency factor F , defined as $1/ED_{10}$, is estimated. ED_{10} is the estimated dose associated with a lifetime cancer risk of 10%. The

potency factor F is used together with the qualitative weight-of-evidence for carcinogenicity in the ranking of the carcinogenic hazard potential of the chemicals.

The potency factor F is used in place of the potency factor $q_1^{*†}$, which the Carcinogen Assessment Group (CAG) normally uses in the estimation of upper bounds of risk, because the objective here is to rank chemicals for their potential to cause carcinogenic harm and not to estimate risk associated with a particular level of exposure. Furthermore, using the potency factor F has the advantage of avoiding the many assumptions that are required for calculating and/or using q_1^* . This is possible because the dose associated with a lifetime cancer risk of 10% is usually within or close to the experimentally observable range.

Other advantages of the potency factor F are:

- a. It is relatively insensitive to the choice of the dose-response extrapolation model.
- b. The point estimation of ED₁₀, which has some optimal statistical properties, can be used to calculate F. Therefore, it is not necessary to use a statistical upper-bound estimate.

POTENCY FACTOR GROUPING

The potency factor estimates are indicators of relative magnitude (potency) to cause carcinogenic harm. These numerical values are useful tools for setting toxicity indexes.

When the relative potency factors are estimated by the procedure outlined above, they are aggregated into four groups. Those chemicals with the highest potency factor are placed in group 1, intermediate potency factor chemicals are

[†] q_1^* is the upper confidence limit for the linear coefficient in the multistage model.

placed in group 2, low potency factor chemicals are placed in group 3, and the lowest potency factor chemicals are placed in group 4. The method used for grouping 192 chemicals for the RQ project is to place chemicals with potency factors (F) above 100 into group 1; chemicals with potency factors from 10-100 into group 2; chemicals with potency factors from 1-10 into group 3; and chemicals with potency factors below 1 into group 4. The major disadvantage of this method is that the grouping of chemicals with borderline potencies between groups is arbitrary. While toxicologic information could be used to aid in placement, the process would still be somewhat subjective. Another method of grouping is analysis for clustering in addition to potency numerical value cut-off points.

CANCER HAZARD RANKING BASED ON COMBINED QUALITATIVE AND QUANTITATIVE ASSESSMENTS

The culmination of the hazard ranking process described in this study is accomplished by combining the qualitative weight-of-evidence for carcinogenicity with the potency group placement to arrive at a final carcinogenicity index for each chemical. Substances are ranked as posing a high, medium, or low cancer hazard according to the following scheme:

Carcinogenicity Indexing for Reportable Quantities under CERCLA

IARC Group	Potency Group			
	1 F>100	2 F = 10-100	3 F = 1-10	4 F<1
1	HIGH	HIGH	MEDIUM	LOW
2A	HIGH	MEDIUM	MEDIUM	LOW
2B	HIGH	MEDIUM	LOW	LOW
3	Cannot Be Ranked in General*			

The hazard rankings for about 200 suspected carcinogens are presented in Table I (page 12).

III. TOXICITY INDEX FOR SUBSTANCES WITH SYSTEMIC (CHRONIC) TOXICITY POTENTIAL

The toxicity indexes on chronic toxicity reflect two primary attributes of each chemical:

1. The minimum effective dose (MED) levels for chronic exposures (mg/day for a 70-kg man) via alternative environmental media (air, water, etc.).
2. Type of effect (liver necrosis, teratogenicity, etc.).

THE MINIMUM EFFECTIVE DOSE (MED)

The dose rating for a given chemical is based upon the MED transformed to values ranging from 1-10 using the graph in Figure 1 (page 27). Substances having an effect at a low dose (i.e., those that are more highly toxic) will be given a high rating on this graph, while those requiring a high dose (less toxic) will be given a low rating. The rating values range from 1 to 10.

RATING POTENTIALLY HAZARDOUS CHEMICALS ACCORDING TO THE SEVERITY OF DISEASE

The effect rating for an individual chemical will range from 1 to 10 depending on severity (Table II, page 28), with 10 being the most severe. These values must be assigned on a chemical-by-chemical basis.

TOXICITY HAZARD RANKING BASED ON THE MED AND THE SEVERITY OF DISEASE

A final Composite Score (CS) which is the chronic toxicity index is deter-

* The group 3 category includes chemicals for which the evidence from animal studies is limited or inadequate, and for which there is no human evidence. For those studies with reliable dose-related data, a potency estimate is determined and a hazard ranking is performed.

mined by multiplying the dose rating by the effect rating. The possible range of CSs is thus 1 to 100. Using this scheme, only those compounds inducing what are judged to be the most severe effects at low levels of exposure would fall into the high toxicity index category.

The following step-by-step text gives additional details for this procedure:

1. Identify subchronic or chronic no observed adverse effect levels (NOAELs), lowest observed adverse effect levels (LOAELs) or frank effect levels (FELs) based on animal or human data from the available literature. Note the dose/exposure and the effect.
2. Convert all NOAELs, LOAELs and FELs to units of mg/kg/day. Inhalation, dietary or drinking water exposure data will be converted to units of mg/kg/day doses based on the methods outlined previously (U.S. EPA, 1980).
3. If the NOAEL, LOAEL or FEL is based on subchronic exposure, a corresponding chronic value will be estimated by dividing the subchronic value by 10 or less.
4. The MEDs based on animal data will be converted to human MEDs using the cubed root of the body weight ratio approximation, and the subsequent value will be multiplied by 70 kg to put the MED in units of mg/day for a 70 kg man.**

**This is based on the assumption that metabolic rate is a function of body weight to the two-thirds power. Thus, the human dose, assuming a body weight of 70 kg, is equal to:

$$\text{animal dose} \times \left(\frac{70 \text{ kg}}{\text{animal weight}} \right)^{2/3}$$

This equation can be rearranged so that the human dose in mg/day equals:

$$\text{animal dose} \times \left(\frac{\text{animal weight}}{70 \text{ kg}} \right)^{1/3} \times 70 \text{ kg}$$

5. Assign a dose rating value (RV_d) to the dose associated with the MED as described in Figure 1.
6. Assign an effect rating value (RV_e) to the effect associated with the MED as described in Table II.
7. Calculate the CS as:

$$CS = RV_d \times RV_e$$

8. If more than one MED can be used to calculate a CS for a route of exposure (oral or inhalation), the MED for the route of exposure which will be used in setting the RQ will be selected by the following criteria:
 - If adequate chronic data are available, disregard MEDs based on subchronic data.
 - If more than one MED remains, select the MED which is based on the "best" data.
 - If considerations of data quality do not lead to the selection of a single MED, the MED resulting in the highest CS for a given route will be used.
9. Having selected a single MED and derived a CS for each route of exposure, the MED used to determine the RQ will be the MED from the route of exposure with the highest CS.
10. The reportable quantities (RQs) are then assigned based on the following relationship to CS:

<u>Composite Score</u> (or chronic toxicity index)	<u>RQ (lbs)</u>
81-100	1
41-80	10
21-40	100
6-20	1000
1-5	5000

The composite scores for about 200 potentially hazardous chemicals are presented in Table III (page 29).

TABLE I. SUMMARY OF HAZARD RANKING FOR POTENTIAL CARCINOGENS

Chemical Name	Chemical (CAS)	Degree of Evidence Humans	Degree of Evidence Animals	Grouping Based on IARC Criteria	Potency Factor Estimate	Potency Group	Hazard Ranking
Acenaphthene	(83-32-9)	Inadequate	Inadequate	3	NA	NA	b
Acenaphthylene	(208-96-8)	Inadequate	Inadequate	3	NA	NA	b
2-Acetylaminofluorene	(53-96-3)	Inadequate	Sufficient	2B	32.00	2	Medium
Acrylonitrile	(107-13-1)	Limited	Sufficient	2A	0.06	4	Low
Aflatoxin B ₁	(1162-65-8)	Limited	Sufficient	2A	10,000.00	1	High
Aldrin	(309-00-2)	Inadequate	Limited	2B	63.00	2	Medium
4-Aminobiphenyl	(92-67-1)	Sufficient	Sufficient	1	87.00	2	High
Amitrole	(61-82-5)	Inadequate	Sufficient	2B	9.20	3	Low
Ammonium bichromate	(7789-09-5)	Inadequate	Inadequate	1 ^b	g	NA	Medium
Ammonium chromate	(7788-98-9)	Inadequate	Inadequate	1 ^g	g	NA	Medium
Anthracene	(120-12-7)	Inadequate	Inadequate	3	NA	NA	b
Arsenic and Compounds	(7440-38-2)	Sufficient	Inadequate	1	130.00	NA	High
Arsenic acid	(7778-39-4)	Limited	Inadequate	2A ^d	d	NA	High
Arsenic disulfide	(1303-32-8)	Limited	Inadequate	2A ^d	d	NA	High
Arsenic trichloride	(7784-34-1)	Limited	Inadequate	2A ^d	d	NA	High

Note: The data herein without additional analysis should not be used for risk assessment purposes.

TABLE I. SUMMARY OF HAZARD RANKING FOR POTENTIAL CARCINOGENS (Continued)

Chemical Name	Chemical (CAS)	Degree of Evidence Humans	Degree of Evidence Animals	Grouping Based on IARC Criteria	Potency Factor Estimate	Potency Group	Hazard Ranking
Arsenic pentoxide	(1303-28-2)	Limited	Inadequate	2A ^d	d	NA	High
Arsenic trioxide	(1327-53-3)	Sufficient	Inadequate	1	130.00	1	High
Arsenic trisulfide	(1303-33-9)	Limited	Inadequate	2A ^d	d	NA	High
Asbestos	(1332-21-4)	Sufficient	Sufficient	1	p	p	p
Auramine	(2465-27-2)	Inadequate	Sufficient	2B	1.20	3	Low
Azaserine	(115-02-6)	Inadequate	Sufficient	2B	a	NA	o
Azifidine	(151-56-4)	Inadequate	Limited	2B	310.00	1	High
Benzene	(71-43-2)	Sufficient	Limited	1	0.26	4	Low
Benzidine and its salts	(92-87-5)	Sufficient	Sufficient	1	1.90	3	Medium
Benzo[a]pyrene	(50-32-8)	Inadequate	Sufficient	2B	500.00	1	High
Benzo[b]fluoranthene	(205-99-2)	Inadequate	Sufficient	2B	150.00 ¹	1	High
Benzo[ghi]perylene	(191-24-2)	Inadequate	Inadequate	3	NA	NA	b
Benzo[k]fluoranthene	(207-08-9)	Inadequate	Limited	3 ^r	NA	NA	c
Benzyl Chloride	(100-44-7)	Inadequate	Limited	3 ^r	NA	NA	o
Benzo[a]anthracene	(56-55-3)	Inadequate	Sufficient	2B	21.00	2	Medium

Note: The data herein without additional analysis should not be used for risk assessment purposes.

TABLE 1. SUMMARY OF HAZARD RANKING FOR POTENTIAL CARCINOGENS (Continued)

Chemical Name	Chemical (CAS)	Degree of Evidence Humans	Degree of Evidence Animals	Grouping Based on IARC Criteria	Potency Factor Estimate	Potency Group	Hazard Ranking
Benzocaine	(225-51-4)	Inadequate	Limited	3 ^r	1500.00	1	Medium
Beryllium and Compounds	(7440-41-7)	Limited	Sufficient	2A ^o	17.00 ^j	2	Medium
Bis(2-chloroethyl) ether	(111-44-4)	Inadequate	Sufficient	2B	13.00	2	Medium
Bis(chloromethyl) ether	(542-88-1)	Sufficient	Sufficient	1	1900.00	1	High
Cacodylic acid	(75-60-5)	Inadequate	Inadequate	3	NA	NA	b
Cadmium and Compounds	(7740-43-9)	Limited	Sufficient	2A ^f	60.00 ^k	2	Medium
Cadmium acetate	(543-90-8)	Limited	Sufficient	2A ^f	k	NA	Medium
Cadmium bromide	(7789-42-6)	Limited	Sufficient	2A ^f	k	NA	Medium
Cadmium chloride	(10108-64-2)	Limited	Sufficient	2A ^f	k	NA	Medium
Cadmium sulfate	(10124-36-4)	Limited	Sufficient	2A ^f	k	NA	Medium
Calcium arsenate	(7778-44-1)	Limited	Inadequate	2A ^d	d	NA	High
Calcium arsenite	(52740-16-6)	Limited	Inadequate	2A ^d	d	NA	High
Calcium chromate	(13765-19-0)	Sufficient	Sufficient	1B	g	NA	Medium
Carbon tetrachloride	(56-23-5)	Inadequate	Sufficient	2B	39.00	2	Medium
Chlorambucil	(305-03-3)	Sufficient	Sufficient	1	a	NA	o

Note: The data herein without additional analysis should not be used for risk assessment purposes.

TABLE 1. SUMMARY OF HAZARD RANKING FOR POTENTIAL CARCINOGENS (Continued)

Chemical Name	Chemical (CAS)	Degree of Evidence Humans	Degree of Evidence Animals	Grouping Based on IARC Criteria	Potency Factor Estimate	Potency Group	Hazard Ranking
Chlordane	(57-74-9)	Inadequate	Limited	3 ^f	83.00	2	Low
Chloronaphazine	(494-03-1)	Sufficient	Limited	1	a	NA	c
Chlorobenzilate	(510-15-6)	Inadequate	Sufficient	2B	1.60	3	Low
Chloroform	(67-66-3)	Inadequate	Sufficient	2B	2.00	3	Low
Chloromethyl methyl ether (technical grade) ⁿ	(107-30-2)	Sufficient ⁿ	Sufficient ⁿ	1	n	n	High ⁿ
Chloromethyl methyl ether	(107-30-2)	Inadequate	Inadequate	3	NA	NA	b
4-Chloro-o-toluidine hydrochloride	(3165-93-3)	Inadequate	Sufficient	2B	0.07	4	Low
Chromium and Compounds	(7440-47-3)	Sufficient	Sufficient	1 ^g	1.90 ^g	3	Medium
Chromic acetate	(1066-30-4)	Inadequate	Inadequate	1 ^g	g	NA	b
Chromic acid	(7738-94-5)	Limited	Inadequate	1 ^g	g	NA	Medium
Chromic sulfate	(10101-53-8)	Inadequate	Inadequate	1 ^g	g	NA	b
Chromous acid	(10049-05-5)	Inadequate	Inadequate	1 ^g	g	NA	b
Chrysene	(218-01-9)	Inadequate	Sufficient	2B	5.00 ^d	3	Low
Creosote	(8001-58-9)	Limited	Sufficient	2A	58.00	2	Medium
Cupric acetoarsenite	(12002-03-8)	Inadequate	Inadequate	2A ^d	d	NA	High

Note: The data herein without additional analysis should not be used for risk assessment purposes.

TABLE 1. SUMMARY OF HAZARD RANKING FOR POTENTIAL CARCINOGENS (Continued)

Chemical Name	Chemical (CAS)	Degree of Evidence Humans Animals	Grouping Based on IARC Criteria	Potency Factor Estimate	Potency Group	Hazard Ranking
Cyclophosphamide	(50-18-0)	Sufficient	Sufficient	1	2	High
Daunomycin	(20830-81-3)	Inadequate	Sufficient	2B	NA	a
DDD	(72-54-8)	Inadequate	Sufficient	2B	4	Low
DDE	(72-55-9)	Inadequate	Sufficient	2B	3	Low
DDT	(50-29-3)	Inadequate	Sufficient	2B	3	Low
Diallate	(2303-16-4)	Inadequate	Sufficient	2B	3	Low
2,4-Diaminotoluene	(95-80-7)	Inadequate	Sufficient	2B	3	Low
1,2,7,8-Dibenzopyrene	(189-55-9)	Inadequate	Sufficient	2B	3	Low
Dibenz[a,h]anthracene	(53-70-3)	Inadequate	Sufficient	2B	NA	a
1,2-Dibromo-3-chloropropane	(96-12-8)	Inadequate	Sufficient	2B	1	High
Dibutyl nitrosamine	(924-16-3)	Inadequate	Sufficient	2B	1	High
3,3'-Dichlorobenzidine	(91-94-1)	Inadequate	Sufficient	2B	2	Medium
1,2-Dichloroethane	(107-06-2)	Inadequate	Sufficient	2B	3	Low
1,1-Dichloroethylene	(75-35-4)	Inadequate	Limited	2B	4	Low
Dichlorophenylarsine	(696-28-6)	Inadequate	Inadequate	3F	3	Low
				3	NA	b

Note: The data herein without additional analysis should not be used for risk assessment purposes.

TABLE 1. SUMMARY OF HAZARD RANKING FOR POTENTIAL CARCINOGENS (Continued)

Chemical Name	Chemical (CAS)	Degree of Evidence Humans	Degree of Evidence Animals	Grouping Based on IARC Criteria	Potency Factor Estimate	Potency Group	Hazard Ranking
Dieldrin	(60-57-1)	Inadequate	Sufficient	2B	130.00	1	High
Diepoxybutane	(1464-53-5)	Inadequate	Sufficient	2B	8.50	3	Low
Diethanolnitrosamine	(1116-54-7)	Inadequate	Sufficient	2B	17.00	2	Medium
Diethyl Arzine	(692-42-2)	Inadequate	Inadequate	3	NA	NA	b
1,2-Diethylhydrazine	(1615-80-1)	Inadequate	Sufficient	2B	a	NA	o
Diethylnitrosamine	(55-18-5)	Inadequate	Sufficient	2B	1000.00	1	High
Diethylstilbestrol	(56-53-1)	Sufficient	Sufficient	1	7900.00	1	High
Dihydrosefrole	(94-58-6)	Inadequate	Sufficient	2B	1.10	3	Low
3,3'-Dimethoxybenzidine	(119-90-4)	Inadequate	Sufficient	2B	0.01	4	Low
Dimethyl sulfate	(77-78-1)	Inadequate	Sufficient	2B	a	NA	o
Dimethylaminosobenzene	(60-11-7)	Inadequate	Sufficient	2B	280.00	1	High
7,12-Dimethylbenz[a]anthracene	(57-97-6)	Inadequate	Sufficient	2B	200,000.00	1	High
Dimethylcarbamoyl chloride	(79-44-7)	Inadequate	Sufficient	2B	510.00	1	High
1,1-Dimethylhydrazine	(57-14-4)	Inadequate	Sufficient	2B	13.00	2	Medium
1,2-Dimethylhydrazine	(540-73-8)	Inadequate	Sufficient	2B	870.00	1	High

Note: The data herein without additional analysis should not be used for risk assessment purposes.

TABLE I. SUMMARY OF HAZARD RANKING FOR POTENTIAL CARCINOGENS (Continued)

Chemical Name	Chemical (CAS)	Degree of Evidence Humans	Degree of Evidence Animals	Grouping Based on IARC Criteria	Potency Factor Estimate	Potency Group	Hazard Ranking
Dimethylnitrosamine	(62-75-9)	Inadequate	Sufficient	2B	29.00	2	Medium
2,3-Dinitrotoluene	(602-01-7)	Inadequate	Inadequate	3	NA	NA	b
2,4-Dinitrotoluene	(121-14-2)	Inadequate	Sufficient	2B	3.00	3	Low
2,5-Dinitrotoluene	(619-15-8)	Inadequate	Inadequate	3	NA	NA	b
2,6-Dinitrotoluene	(606-20-2)	Inadequate	Limited	3 ^r	NA	NA	a
3,4-Dinitrotoluene	(610-39-9)	Inadequate	Inadequate	3	NA	NA	b
1,4-Dioxane	(123-91-1)	Inadequate	Sufficient	2B	0.03	4	Low
N,N-Diphenylamine	(122-39-4)	Inadequate	Inadequate	3	NA	NA	b
1,2-Diphenylhydrazine	(122-66-7)	Inadequate	Sufficient	2B	4.60	3	Medium
Dipropylnitrosamine	(621-64-7)	Inadequate	Sufficient	2B	a	NA	a
Epichlorohydrin	(106-89-8)	Inadequate	Sufficient	2B	0.16	4	Low
Ethyl Methanesulfonate	(62-50-0)	Inadequate	Sufficient	2B	140.00	1	High
Ethylene dibromide	(106-93-4)	Inadequate	Sufficient	2B	13.00	2	Medium
Ethylene Oxide	(75-21-8)	Limited	Limited	2A	6.00	3	Medium
Ethylmethiourea	(96-45-7)	Inadequate	Sufficient	2B	0.97	4	Low

Note: The data herein without additional analysis should not be used for risk assessment purposes.

TABLE I. SUMMARY OF HAZARD RANKING FOR POTENTIAL CARCINOGENS (Continued)

Chemical Name	Chemical (CAS)	Degree of Evidence Humans	Degree of Evidence Animals	Grouping Based on IARC Criteria	Potency Factor Estimate	Potency Group	Hazard Ranking
1-Ethyl-3-nitrosourea	(759-73-9)	Inadequate	Sufficient	2B	8.70	3	Low
Ferrie dextran	(9004-66-4)	Inadequate	Sufficient	2B	0	NA	b
Fluoranthene	(206-44-0)	Inadequate	Inadequate	3	NA	NA	b
Fluorene	(86-73-7)	Inadequate	Inadequate	3	NA	NA	b
Oxycidaldehyde	(765-34-4)	Inadequate	Sufficient	2B	1.20	3	Medium
Heptachlor	(76-44-8)	Inadequate	Sufficient	2B	36.00	2	Medium
Heptachlor Epoxide	(1024-57-3)	Inadequate	Sufficient	2B	36.00 ⁹	2	Medium
Hexachlorobenzene	(118-74-1)	Inadequate	Sufficient	2B	12.00	2	Medium
Hexachlorobutadiene	(87-68-3)	Inadequate	Limited	3 ^r	0.50	4	Low
α -Hexachlorocyclohexane	(319-84-6)	Inadequate	Sufficient	2B	211.00	1	High
β -Hexachlorocyclohexane	(319-85-7)	Inadequate	Limited	3 ^r	1.70	3	Low
γ -Hexachlorocyclohexane	(58-89-9)	Inadequate	Limited	2B	1.70	3	Low
δ -Hexachlorocyclohexane	(319-86-8)	Inadequate	Inadequate	3	NA	NA	b
Hexachloroethane	(67-72-1)	Inadequate	Limited	3 ^r	0.27	4	Low
Hydrazine	(302-01-1)	Inadequate	Sufficient	2B	100.00	1	High

Note: The data herein without additional analysis should not be used for risk assessment purposes.

TABLE I. SUMMARY OF HAZARD RANKING FOR POTENTIAL CARCINOGENS (Continued)

Chemical Name	Chemical (CAS)	Degree of Evidence Humans	Degree of Evidence Animals	Grouping Based on IARC Criteria	Potency Factor Estimate	Potency Group	Hazard Ranking
Indeno(1,2,3-cd)pyrene	(193-39-5)	Inadequate	Limited	2B	a	NA	c
Iodomethane	(77-08-4)	Inadequate	Limited	3 ^F	NA	NA	c
Isosafrole	(120-58-1)	Inadequate	Limited	3 ^F	0.54	4	Low
Kepone	(143-50-0)	Inadequate	Sufficient	2B	44.00	2	Medium
Lasiocarpine	(303-34-4)	Inadequate	Sufficient	2B	38.00	2	Medium
Lead acetate	(301-04-2)	Inadequate	Sufficient	2B	7.30	3	Low
Lead arsenate	(3687-31-8)	Limited	Inadequate	2A ^d	d	NA	High
Lead phosphate	(7446-27-7)	Inadequate	Limited	2B	a	NA	c
Lead subacetate	(1335-32-6)	Inadequate	Sufficient	2B	0.17	4	Low
Lithium chromate	(14307-35-8)	Inadequate	Inadequate	1 ^B	8	NA	Medium
3-Methylcholanthrene	(56-49-3)	Inadequate	Sufficient	2B	12.00	3	Medium
4,4'-Methylene-bis-(2-chloroaniline)	(101-14-4)	Inadequate	Sufficient ^e	2B	1.70	3	Low
Methylnitrosourea	(684-93-5)	Inadequate	Sufficient	2B	12,000.00	1	High
Methylthiourea	(56-04-2)	Inadequate	Sufficient	2B	30.00	2	Medium
Methylvinylnitrosamine	(4549-40-0)	Inadequate	Sufficient	2B	a	NA	c

Note: The data herein without additional analysis should not be used for risk assessment purposes.

TABLE I. SUMMARY OF HAZARD RANKING FOR POTENTIAL CARCINOGENS (Continued)

Chemical Name	Chemical (CAS)	Degree of Evidence Humans	Degree of Evidence Animals	Grouping Based on IARC Criteria	Potency Factor Estimate	Potency Group	Hazard Ranking
N-Methyl-N'-nitro-N-nitrosoguanidine	(70-25-7)	Inadequate	Sufficient	2B	58.00	2	Medium
Mitomycin C	(50-07-7)	Inadequate	Sufficient	2B	a	NA	c
Mustard gas	(505-60-2)	Sufficient	Limited	1	a	NA	c
1-Naphthylamine	(134-32-7)	Inadequate	Limited	3 ^r	NA	NA	c
2-Naphthylamine	(91-59-8)	Sufficient	Sufficient	1	5.20	3	Medium
Nickel and Compounds	(7440-02-0)	Limited	Sufficient	2A ^h	1.10 ¹	3	Medium
Nickel Ammonium Sulfate	(15699-18-0)	Limited	Limited	2A ^h	1	NA	Medium
Nickel carbonyl	(13463-39-3)	Limited	Sufficient	2A ^h	1	NA	Medium
Nickel chloride	(7718-54-9)	Limited	Limited	2A ^h	1	NA	Medium
Nickel cyanide	(557-19-7)	Limited	Limited	2A ^h	1	NA	Medium
Nickel hydroxide	(12054-48-7)	Limited	Limited	2A ^h	1	NA	Medium
Nickel nitrate	(13478-00-7)	Limited	Limited	2A ^h	1	NA	Medium
Nickel subsulfide	(12035-72-2)	Limited	Sufficient	2A ^h	1.10 ¹	1	Medium
Nickel sulfate	(7786-81-4)	Limited	Limited	2A ^h	1	NA	Medium
Nitrosomethylurethane	(615-53-2)	Inadequate	Sufficient	2B	2400.00	1	High

Note: The data herein without additional analysis should not be used for risk assessment purposes.

TABLE I. SUMMARY OF HAZARD RANKING FOR POTENTIAL CARCINOGENS (Continued)

Chemical Name	Chemical (CAS)	Degree of Evidence Humans	Degree of Evidence Animals	Grouping Based on IARC Criteria	Potency Factor Estimate	Potency Group	Hazard Ranking
N-Nitrosopiperidine	(100-75-4)	Inadequate	Sufficient	2B	170.00	1	High
N-Nitrosopyrrolidine	(930-55-2)	Inadequate	Sufficient	2B	290.00	1	High
5-Nitro-o-toluidine	(99-55-8)	Inadequate	Limited	3 ^F	0.53	4	Low
Pentachloronitrobenzene	(82-68-8)	Inadequate	Limited	3 ^F	1.50	3	Low
Phenacetin	(62-44-2)	Inadequate	Sufficient	2B	0.02	4	Low
Phenanthrene	(85-01-8)	Inadequate	Inadequate	3	NA	NA	b
Phenobarbital	(50-06-6)	Inadequate	Limited	3 ^F	0.75	4	Low
Phenylalanine Mustard	(148-82-3)	Sufficient	Sufficient	1	1100.00	1	High
Polychlorinated biphenyls	(1336-36-3)	Inadequate	Sufficient	2B	37.00 ^m	2	Medium
Potassium arsenate	(7784-41-0)	Limited	Inadequate	2A ^d	d	NA	High
Potassium arsenite	(10124-50-2)	Limited	Inadequate	2A ^d	d	NA	High
Potassium bichromate	(7778-50-9)	Limited	Inadequate	1B	g	NA	Medium
Potassium chromate	(7789-00-6)	Limited	Inadequate	1B	g	NA	Medium
Propene sulfone	(1120-71-4)	Inadequate	Sufficient	2B	37.00	2	Medium
Propyleneimine	(75-55-8)	Inadequate	Sufficient	2B	15.00	2	Medium

Note: The data herein without additional analysis should not be used for risk assessment purposes.

TABLE 1. SUMMARY OF HAZARD RANKING FOR POTENTIAL CARCINOGENS (Continued)

Chemical Name	Chemical (CAS)	Degree of Evidence Humans	Degree of Evidence Animals	Grouping Based on IARC Criteria	Potency Factor Estimate	Potency Group	Hazard Ranking
Pyrene	(129-00-0)	Inadequate	Inadequate	3	NA	NA	b
Saccharin	(81-07-2)	Inadequate	Limited	3 ^r	0.01	4	Low
Safrole	(94-59-7)	Inadequate	Sufficient	2B	0.20	4	Low
Sodium arsenate	(7631-89-2)	Limited	Inadequate	2A ^d	d	NA	High
Sodium arsenite	(7784-46-5)	Limited	Inadequate	2A ^d	d	NA	High
Sodium bichromate	(10588-01-9)	Limited	Inadequate	1B	g	NA	Medium
Sodium chromate	(7775-11-3)	Limited	Inadequate	1B	g	NA	Medium
Streptozotocin	(16883-66-4)	Inadequate	Sufficient	2B	110.00	1	High
Strontium chromate	(7789-06-2)	Inadequate	Inadequate	1B	g	NA	Medium
2,3,7,8-Tetrachloro-dibenzo-p-dioxin	(1746-01-6)	Inadequate	Sufficient	2B	120,000.00	1	High
1,1,1,2-Tetrachloroethane	(630-20-6)	Inadequate	Limited	3	0.13	4	Low
1,1,2,2-Tetrachloroethane	(79-34-5)	Inadequate	Limited	3 ^r	1.70	4	Low
Tetrachloroethylene	(127-18-4)	Inadequate	Limited	3 ^r	0.18	4	Low
Thioacetamide	(62-55-5)	Inadequate	Sufficient	2B	27.00	2	Medium
Thiourea	(62-56-6)	Inadequate	Sufficient	2B	80.00	2	Medium

Note: The data herein without additional analysis should not be used for risk assessment purposes.

TABLE 1. SUMMARY OF HAZARD RANKING FOR POTENTIAL CARCINOGENS (Continued)

Chemical Name	Chemical (CAS)	Degree of Evidence Humans	Degree of Evidence Animals	Grouping Based on IARC Criteria	Potency Factor Estimate	Potency Group	Hazard Ranking
O-Tolidine	(119-93-7)	Inadequate	Sufficient	2B	27.00	2	Medium
O-Tolidine and its hydrochloride	(636-21-5)	Limited	Sufficient	2A	0.22	4	Low
Toluene	(8001-35-2)	Inadequate	Sufficient	2B	9.70	3	Low
1,1,2-Trichloroethane	(79-00-5)	Inadequate	Limited	3 ^r	0.30	4	Low
Trichloroethylene	(79-01-6)	Inadequate	Limited	3 ^r	0.18	4	Low
2,4,6-Trichlorophenol	(88-06-2)	Inadequate	Sufficient	2B	0.08	4	Low
Tris(2,3-dibromopropyl) phosphate	(126-72-7)	Inadequate	Sufficient	2B	9.80	3	Low
Trypan blue	(72-57-1)	Inadequate	Sufficient	2B	0.01	4	Low
Ureol Mustard	(66-75-1)	Inadequate	Sufficient	2B	a	NA	0
Urethane	(51-79-6)	Inadequate	Sufficient	2B	0.64	4	Low
Vinyl chloride	(75-01-4)	Sufficient	Sufficient	1	0.16	4	Low

Note: The data herein without additional analysis should not be used for risk assessment purposes.

TABLE 1. SUMMARY OF HAZARD RANKING FOR POTENTIAL CARCINOGENS (Continued)

Chemical Name	Chemical (CAS)	Degree of Evidence Humans Animals	Grouping Based on IARC Criteria	Potency Factor Estimate	Potency Group	Hazard Ranking
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^aData available are inadequate for calculation of potency factor using current methodology. An appropriate method of estimating a potency factor for these types of data is currently under development by CAG.

^bOther toxicity endpoints must be used as a basis for hazard ranking.

^cCarcinogen hazard ranking will be possible when methodology to calculate a reasonable potency factor is developed or new data becomes available.

^dGrouping and potency factor estimate is based on weight of evidence for arsenic and arsenic compounds in the drinking water of humans (assumed to be predominantly the trioxide).

^eGrouping is based on weight of evidence for beryllium sulfate.

^fGrouping is based on weight of evidence for cadmium compounds as a class.

^gGrouping is based on weight of evidence for chromate production and animal data which indicates that hexavalent chromium is carcinogenic. The potency estimate is based on epidemiology data for total chromium exposure of chromate workers..

^hGrouping is based on weight of evidence for nickel compounds as a class.

ⁱCalculated, using the potency factor estimate for benzo(a)pyrene as a reference.

^jPotency estimate is based on data from beryllium sulfate exposure in rats.

^kPotency estimate is based on epidemiology data¹ for cadmium smelters. Please note that potency estimate based on animal data would be at least 100 times higher. Please refer to OMEA document "Addendum to the Health Assessment Document for Cadmium, 1983" for details.

^lPotency estimate is based on data for nickel subsulfide.

^mPotency estimate is based on data for Aroclor 1260.

ⁿTechnical grade chloromethyl methyl ether is contaminated with bis(chloromethyl) ether, and the hazard ranking is therefore based on the evidence for bis(chloromethyl) ether.

^oInappropriate to group or rank for environmental considerations because available evidence is based on subcutaneous and intramuscular injection experiments.

^pA potency factor estimate for asbestos is inappropriate here because the carcinogenic potential of asbestos is related to specific fiber shapes, sizes, and atmospheric concentrations. Air concentrations are usually measured either as number of fibers or mass. However, no direct relationship exists between air fiber/m³ (>5 microns) concentrations (by the phase contrast light microscope method) and mass concentrations in µg/m³ (determined by electron microscopy). The relationship depends on the type of environment sampled, the type of asbestos in the air, and the size of the fibers.

^qPotency factor estimate is based on data for heptachlor since heptachlor epoxide is a metabolite of heptachlor.

^rThe Group 3 category includes chemicals for which the evidence from animal studies is limited or inadequate and there is no human evidence. These are group 3 chemicals with limited animal evidence. For those with good dose-related data, a potency estimate is determined and a hazard ranking is performed.

^sCompounds with group 1 potency factor estimates (>100) are given "medium" hazard ranking. Compounds in potency group 2, 3 or 4 are given "low" hazard rankings.

NA = Not applicable

TABLE I. SUMMARY OF HAZARD RANKING FOR POTENTIAL CARCINOGENS (Continued)

The substances identified for re-evaluation and profile revision are:

hexachlorocyclohexane
sodium arsenite
N-nitrosodiethanolamine
DDE
dibutyl nitrosamine
dipropyl nitrosamine
N,N-diphenylamine
cadmium chloride
amitrole
thioacetamide
N-nitrosodiethanolamine
mustard gas
phenacetin
benzene

Note: The data herein without additional analysis should not be used for risk assessment purposes.

RATING VALUES FOR DOSES

$RV_d = 10$ IF $\text{LOG MED} < -3$
 $RV_d = -1.5 \text{ LOG MED} + 5.5$ IF $-3 < \text{LOG MED} < 3$
 $RV_d = 1$ IF $\text{LOG MED} > 3$

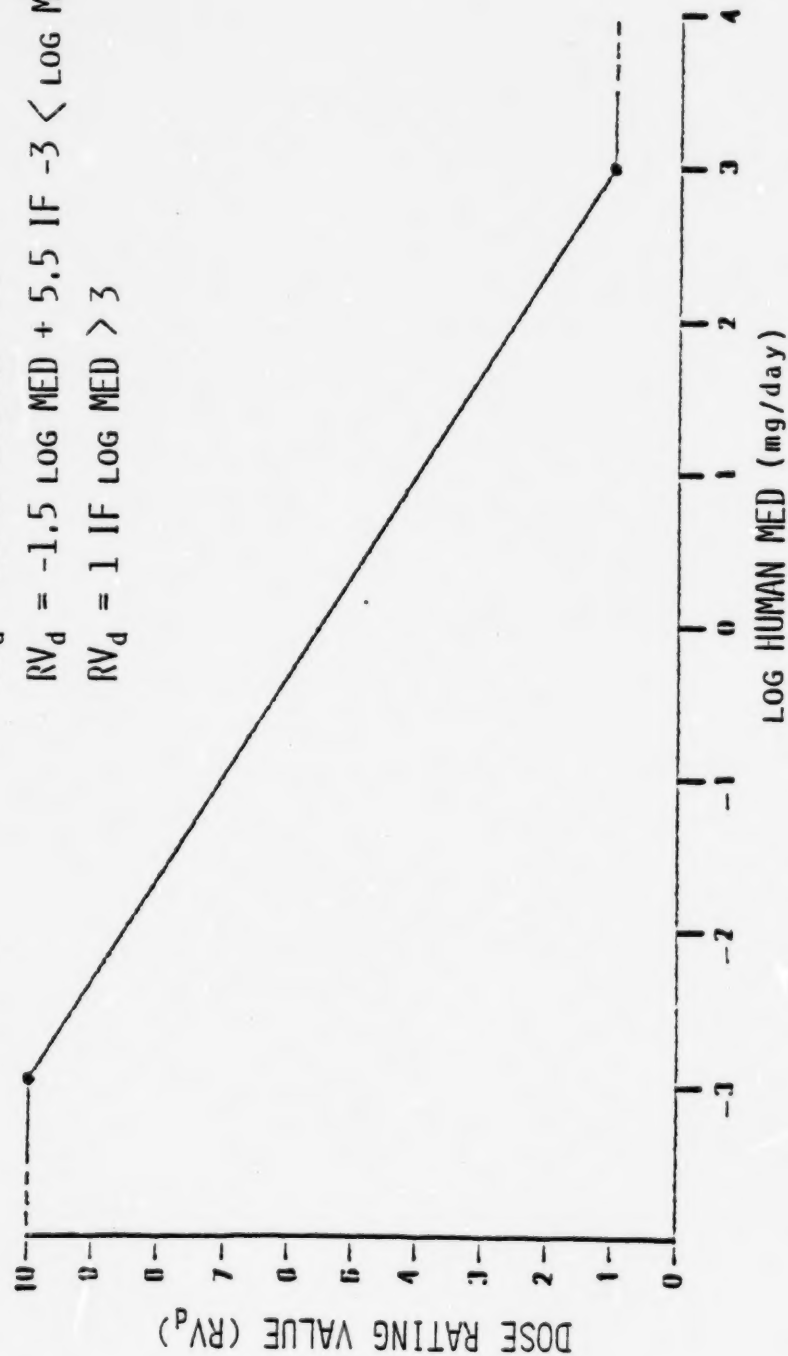


FIGURE 1. RATING VALUES FOR DOSES USED TO DERIVE REPORTABLE QUANTITIES BASED ON CHRONIC TOXICITY.

TABLE II. SEVERITY OF DISEASE RATING VALUES FOR NOELS, LOELS, AND FELS
USED TO DERIVE REPORTABLE QUANTITIES BASED ON CHRONIC TOXICITY

RATING VALUE RV _e	EFFECT
1	ENZYME INDUCTION OR OTHER BIOCHEMICAL CHANGE WITH NO PATHOLOGIC CHANGES AND NO CHANGE IN ORGAN WEIGHTS
2	ENZYME INDUCTION AND SUBCELLULAR PROLIFERATION OR OTHER CHANGES IN ORGANELLES BUT NO OTHER APPARENT EFFECTS.
3	HYPERPLASIA, HYPERTROPHY, OR ATROPHY BUT NO CHANGE IN ORGAN WEIGHTS.
4	HYPERPLASIA, HYPERTROPHY, OR ATROPHY WITH CHANGES IN ORGAN WEIGHTS.
5	REVERSIBLE CELLULAR CHANGES: CLOUDY SWELLING, HYDROPIC CHANGE, OR FATTY CHANGES.
6	NECROSIS OR METAPLASIA WITH NO APPARENT DECREMENT OF ORGAN FUNCTION. ANY NEUROPATHY WITHOUT APPARENT BEHAVIORAL, SENSORY, OR PHYSIOLOGIC CHANGES.
7	NECROSIS, ATROPHY, HYPERTROPHY, OR METAPLASIA WITH A DETECTABLE DECREMENT OF ORGAN FUNCTIONS. ANY NEUROPATHY WITH A MEASURABLE CHANGE IN BEHAVIORAL, SENSORY, OR PHYSIOLOGIC ACTIVITY.
8	NECROSIS, ATROPHY, HYPERTROPHY, OR METAPLASIA WITH DEFINITIVE ORGAN DYSFUNCTION. ANY NEUROPATHY WITH GROSS CHANGES IN BEHAVIOR, SENSORY, OR MOTOR PERFORMANCE. ANY DECREASE IN REPRODUCTIVE CAPACITY. ANY EVIDENCE OF FETOTOXICITY.
9	PRONOUNCED PATHOLOGIC CHANGES WITH SEVERE ORGAN DYSFUNCTION. ANY NEUROPATHY WITH LOSS OF BEHAVIORAL OR MOTOR CONTROL OR LOSS OF SENSORY ABILITY. REPRODUCTIVE DYSFUNCTION. ANY TERATOGENIC EFFECT WITH MATERNAL TOXICITY.
10	DEATH OR PRONOUNCED LIFE SHORTENING. ANY TERATOGENIC EFFECT WITHOUT SIGNS OF MATERNAL TOXICITY.

TABLE III. SUMMARY OF HAZARD RANKING BASED ON CHRONIC TOXICITY

Chemical	Route	Dose ^a (mg/day)	Effect	RV _d ^b	RV _e	Composite ^b Score	RQ	Reference
Acenaphthene							10	
Acetic acid, lead salt (lead acetate)	oral	35.2	Decrease in survival of offspring	3.2	10	32	100	By analogy to lead (and compounds)
Acetic acid, thallium (I) salt [thallium (I) acetate]	oral	0.90	Alopecia, increased kidney weight	5.6	4	22	100	Downs et al., 1960
Acetonitrile	inhalation	115	Neurological disorders and hemorrhages in the brain	2.4	8	19	1000	Pozzani et al., 1959
Acrylonitrile	oral	29.9	Teratogenicity with maternal toxicity	3.3	9	30	100	Murray et al., 1976
Allyl alcohol	inhalation	3.54	Focal necrosis of liver and kidney	4.7	6	28	100	Torkelson et al., 1959
Ammonia	inhalation	42.5	Hydropic changes in adrenal glands, cloudy swelling in kid- ney tubules, increased splenic hemosiderin	3.1	5	15	1000	Weatherby, 1952
Ammonium bichromate							10	
Ammonium bifluoride	oral	12	Mottled teeth resulting from fluoride moiety	3.9	5	19	1000	U.S. EPA, 1980
Ammonium silicofluoride							10	
Antimony (metallic)							10	
Antimony (and compounds)	inhalation (antimony trisulfide)	0.7 of Sb	Altered ECG patterns possibly in- dicating greater susceptibility to heart failure	5.7	8	46	10	Brieger et al., 1954
Antimony potassium tartrate	oral	12.8	Shortening of life span	3.8	10	38	100	Schroeder et al., 1970
Antimony pentachloride							10	
Antimony tribromide							10	

TABLE III. SUMMARY OF HAZARD RANKING BASED ON CHRONIC TOXICITY (Continued)

Chemical	Route	Dose ^a (mg/day)	Effect	RV _D ^b	RV _E	Composite ^b Score	RQ	References
Antimony trichloride							10	
Antimony trifluoride							10	
Antimony trioxide	inhalation	132	Histologic alterations of the lung producing greater susceptibility to pneumonia	2.3	8	18	1000	Gross et al., 1955
Arsenic (metallic)							10	
Arsenic (and compounds)	oral	1.0	Hyperpigmentation and hyperkeratosis of skin, arteriosclerotic gangrene of extremities	5.5	9	50	10	Iseng et al., 1968; Iseng, 1977
Arsenic acid	oral	297	Decreased survival; enlargement, fibrosis, and lesions of common bile duct	1.8	10	18	1000	By analogy to sodium arsenate
Arsenic disulfide							10	
Arsenic (III) oxide	oral	0.114	Hepatic cloudy swelling and spotty necrosis, bile duct proliferation with angitis and fibrosis, sloughing of renal tubular epithelium	6.9	6	41	10	Ishinishi et al., 1980
Arsenic (V) oxide	oral	238	Decreased survival; enlargement, fibrosis, and lesions of common bile duct	1.9	10	19	1000	By analogy to sodium arsenate
Arsenic trichloride	oral	0.216	Hepatic cloudy swelling and spotty necrosis, bile duct proliferation with angitis and fibrosis, sloughing of renal tubular epithelium	6.5	6	39	100	By analogy to arsenic (III) oxide
Arsenic trisulfide	oral	5.15	Polynuropathy, hyperpigmentation and hyperkeratosis of skin	4.4	8	35	100	Tay and Seah, 1975
Arsine, diethyl-							10	
Asbestos	inhalation	0.027	Asbestosis	7.9	10	79	10	Gillam et al., 1976
1,2-Benzanthracene							10	

TABLE III. SUMMARY OF HAZARD RANKING BASED ON CHRONIC TOXICITY (Continued)

Chemical	Route	Dose ^a (mg/day)	Effect	RV _d ^b	RV _e	Composite Score ^b	RQ	References
Benzene	Inhalation	345	Decrease in survival, marked effects on hematopoietic system	1.7	10	17	1000	Green et al., 1981
Benzene, 1,3-dichloro-	Inhalation	277	Increased liver and kidney weight, hepatocellular cloudy swelling	1.8	5	9	1000	By analogy to di-chlorobenzene (a,4-)
Benzene, hexachloro-	oral	50	Increased mortality	3.0	10	30	100	Cam and Migogosyan, 1963
Benzene, hydroxy-(phenol)	Inhalation	20.8	Death	3.5	10	35	100	Deichmann et al., 1944
Benzene, 1-methyl-2,4-dinitro-(2,4-dinitrotoluene)	oral	46.7	Shortening of lifespan, anemia, aspermatogenesis	3.0	10	30	100	Lee et al., 1978
Benzene, 1-methyl-2,6-dinitro-(2,6-dinitrotoluene)	oral	29.9	Methemoglobinemia, anemia, Inco-ordination, CNS demyelination, gliosis, testicular atrophy with aspermatogenesis	3.3	9	30	100	Ellis et al., 1976
Benzene, nitro-							10	
Benzene, pentachloro-	oral	215	Tremors in pups	2.0	7	14	1000	Linder et al., 1980
Benzene, pentachloro-nitro-	oral	479	Kidney lesions	1.5	7	10	1000	Fytizas-Danielidou, 1975
1,2-Benzenedi-carboxylic acid, dibutyl ester (dibutyl phthalate)	oral	420	Fetotoxicity (evidence of delayed ossification)	1.6	8	13	1000	Shiota et al., 1980
1,2-Benzenedi-carboxylic acid, diethyl ester (diethyl phthalate)	oral	29,925	Weight loss	1.0	4	4	5000	Food Research Labs, Inc., 1955
Benzidine	oral	22.4	Hepatic foci of cellular altera-tion	3.5	8	28	100	Frith et al., 1980
Benzo(b)fluoranthene							10	
3,4-Benzopyrene	oral	0.6	Fetotoxicity without maternal toxicity	5.8	8	46	10	Rigdon and Rennels, 1964

TABLE III. SUMMARY OF HAZARD RANKING BASED ON CHRONIC TOXICITY (Continued)

Chemical	Route	Dose ^a (mg/day)	Effect	RV _d ^b	RV _e	Composite ^b Score	RQ	References
p-Benzquinone							10	
1,2-Benzphenanthrene							10	
Beryllium (metallic)							10	
Beryllium (and compounds)	Inhalation	0.011	Chronic pneumonitis, epithelial hyperplasia	8.5	8	68	10	Vorwald and Reeves, 1959
Beryllium chloride	Inhalation	0.594	Increased lung weight, pneumonitis, epithelial hyperplasia	5.8	8	47	10	By analogy to beryllium and compounds
Beryllium fluoride	Inhalation	0.350	Increased lung weight, pneumonitis, epithelial hyperplasia	6.2	8	50	10	By analogy to beryllium and compounds
Beryllium nitrate	Inhalation	0.983	Increased lung weight, pneumonitis, epithelial hyperplasia	5.5	8	44	10	By analogy to beryllium and compounds
(1,1'-Biphenyl)-4,4'-diamine, 3,3'-dichloro- (dichlorobenzidine)							10	
Bis(2-chloroisopropyl) ether	oral	743	Decreased survival	1.2	10	12	1000	NCI, 1979
Bis(chloromethyl) ether							10	
1,3-Butadiene, 1,1,2,3,4,4-hexachloro-	diet	23.9	Increased urinary coproporphyrin and renal hyperplasia	3.4	3	10	1000	Kociba et al., 1977
2-Butanone (methyl ethyl ketone)	Inhalation	860	Fetotoxicity	1.1	8	8	1000	Schuetz et al., 1974
Cadmium (metallic)							10	
Cadmium (and compounds)	Inhalation	0.075 as Cd	Pulmonary and renal dysfunction	7.2	8	58	10	Lauwerys et al., 1974
Cadmium acetate	oral	9.18	Decreased survival	4.1	10	41	10	Schroeder et al., 1964
Cadmium bromide	oral	0.65	Necrosis of renal tubular epithelium	5.8	7	41	10	By analogy to cadmium chloride

TABLE III. SUMMARY OF HAZARD RANKING BASED ON CHRONIC TOXICITY (Continued)

Chemical	Route	Dose ^a (mg/day)	Effect	RV _d ^b	RV _e	Composite ^b Score	RQ	Reference
Cadmium chloride	oral	0.44	Necrosis of renal tubular epithelium, decreased immunologic response	6.0	7	42	10	Koller et al., 1975
Calcium arsenate	oral	3.3	Polyneuropathy	4.7	7	33	100	Tay and Seah, 1975
Calcium arsenite	oral	10.8	Decreased survival	3.9	10	39	100	By analogy to sodium arsenite
Calcium chromate	Inhalation	19.3	Epithelial necrosis, atrophy, and hyperplasia of the bronchial tree; emphysema-like changes and focal scarring in alveoli of some mice	3.6	8	29	100	Nettesheim et al., 1971
Captan	oral	251.3	Teratogenicity with maternal toxicity	1.9	9	17	1000	Robens, 1970
Carbamimidioselenonic acid (selenourea)							10	
Carbon disulfide (carbon bisulfide)	Inhalation	33	Decreased immunological reactivity, altered menstrual cycle	3.2	7	23	100	Kashin, 1965; Vasilyeva, 1973
Carbon tetrachloride	Inhalation	17.9	Reduced corneal sensitivity	3.6	7	25	100	Rebber, 1973
Carbonic acid, dithallium (I) salt [thallium (I) carbonate]	oral	0.80	Alopecia, increased kidney weight	5.6	4	23	100	By analogy to thallium I acetate
Chloral (hydrate)							10	
1-Chloro-2,3-epoxypropane	Inhalation	16.9	Squamous metaplasia of nasal turbinates	3.7	7	26	100	Quast et al., 1979a,b
Chlorodibromomethane (dibromochloromethane)	oral	6.6	Suppression of hepatic and splenic phagocytosis	4.3	6	26	100	Hunson et al., 1978
Chloroethane							10	
Chloromethyl methyl ether	Inhalation	5.9	Bronchial hyperplasia and squamous metaplasia	4.3	7	30	100	Laksin et al., 1975

TABLE III. SUMMARY OF HAZARD RANKING BASED ON CHRONIC TOXICITY (Continued)

Chemical	Route	Dose ^a (mg/day)	Effect	RV _d ^b	RV _e	Composite ^b Score	RQ	Reference
2-Chlorophenol (2-monochlorophenol)							10	
Chronic acetate							10	
Chronic acid	Inhalation	1.6	Perforation of the nasal septum	5.2	6	31	100	NIOSH, 1973
Chronic sulfate							10	
Chromium (metallic)							10	
Chromium (and compounds)	Inhalation	6.4	Epithelial necrosis, atrophy, hyperplasia in bronchial tree; emphysema-like changes and focal scarring in alveoli of some mice	4.3	8	34	100	Nettesheim et al., 1971
Chromous chloride							10	
Cobaltous bromide							10	
Cobaltous formate							10	
Cobaltous sulfamate							10	
Copper (metallic)							10	
Copper (and compounds)	oral	14	Elevated serum aspartate trans-aminase levels, jaundice	3.8	5	19	1000	Suttle and Mills, 1966b
Copper sulfate, ammoniated	oral	54	Elevated serum aspartate trans-aminase levels, jaundice	2.9	5	15	1000	By analogy to copper (and compounds)
Cresote	oral	1,496	Decreased food consumption	1.0	1	1	5000	Miyazato et al., 1981
Cresol	Inhalation	1.34	Bone marrow depression of erythroid series	5.3	4	21	100	Uzhdavini et al., 1972
Cupric acetate	oral	44	Elevated serum aspartate trans-aminase levels, jaundice	3.0	5	15	1000	By analogy to copper (and compounds)
Cupric acetoarsenite							10	
Cupric chloride	oral	30	Elevated serum aspartate trans-aminase levels, jaundice	3.3	5	16	1000	By analogy to copper (and compounds)

TABLE III. SUMMARY OF HAZARD RANKING BASED ON CHRONIC TOXICITY (Continued)

Chemical	Route	Dose ^a (mg/day)	Effect	RV _d ^b	RV _e	Composite ^b Score	RQ	Reference
Cupric nitrate	oral	65.2	Elevated serum aspartate trans-aminase levels, jaundice	2.8	5	14	1000	By analogy to copper (and compounds)
Cupric oxalate							10	
Cupric sulfate	oral	35.6 CuSO ₄ ?	Elevated serum aspartate trans-aminase levels, jaundice	3.2	5	16	1000	Suttle and Mills, 1966
Cupric tartrate	oral	47	Elevated serum aspartate trans-aminase levels, jaundice	3.0	5	15	1000	By analogy to copper (and compounds)
2,4-Dichlorophenoxy-acetic acid and (2,4-D esters)	oral	129 (as 2,4-D)	Fetotoxicity	2.3	8	18	1000	Schwetz et al., 1971
Dibenz(a,h)anthracene							10	
Dichlorobenzene (1,2-)	oral	154	Increased liver and kidney weight	2.2	4	8	1000	Hollingsworth et al., 1958
Dichlorobenzene (1,4-)	Inhalation	277	Increased liver and kidney weight, hepatocellular cloudy swelling	1.8	5	9	1000	Hollingsworth et al., 1956
1,2-Dichloroethane	Inhalation	145	Liver and gall bladder diseases	2.3	8	18	1000	Kozik, 1957
1,1-Dichloroethane	Inhalation	542	Kidney injury evidenced by histological changes and increased blood urea	1.4	7	9	1000	Hofmann et al., 1971
1,1-Dichloroethylene (vinylidene chloride)	oral	37.7	Increased incidence of liver necrosis	3.1	6	19	1000	NTP, 1982
1,2-Dichloroethylene	Inhalation	189	Fat accumulation in the liver and histologic changes in the lung	2.1	5	10	1000	Freundt et al., 1977
Dichloromethane	Inhalation	21,750	Increased mortality	1.0	10	10	1000	Burek et al., 1980
2,4-Dichlorophenol	oral	121	Non-specific hepatic changes--swelling of hepatocytes with some differences in cell size and infiltration of round cells	2.4	5	12	1000	Kobayashi et al., 1972
2,6-Dichlorophenol							10	
Dichlorophenylarsine							10	

TABLE III. SUMMARY OF HAZARD RANKING BASED ON CHRONIC TOXICITY (Continued)

Chemical	Route	Dose ^a (mg/day)	Effect	RV _d ^b	RV _e	Composite ^b Score	RQ	Reference
Dichloropropane							10	
1,2-Dichloropropane							10	
Dichloropropane-Dichloropropene mixture	Inhalation	43.8	Increased relative kidney and liver weight	3.0	4	12	1000	Parker et al., 1982
1,3-Dichloropropene	Inhalation	3.24	Slight cloudy swelling of renal tubular epithelium	4.7	5	24	100	Torkelson and Oylen, 1977
Dichloropropene(s)	Inhalation	3.24	Slight cloudy swelling of renal tubular epithelium	4.7	5	24	100	Torkelson and Oylen, 1977
Diethylamine	Inhalation	30.2	Pulmonary irritation, multiple punctate corneal erosions and edema, and histological changes in liver	3.3	8	26	100	Brieger and Hudes, 1951
0,0-Dimethyl-0-p-nitrophenyl phosphorothioate (methyl parathion)	oral	10.7	Decreased survival	4.0	10	40	100	HCI, 1979
Dimethylamine	Inhalation	37	Necrosis of liver parenchymal cells, hepatic fatty degeneration, tubular degeneration of testes, corneal injury	3.1	6	19	1000	Dow Chemical Co., 1964
Dinitrobenzenes	oral	3.0	Testicular atrophy with indications of possible loss of function	4.8	7	34	100	Cody et al., 1981
4,6-Dinitro-o-cresol	oral	2.45	Cataracts	4.9	8	39	100	U.S. EPA, 1980; NIOSH, 1978; Horner, 1942
Dinitrophenols	oral	14	Cataracts	3.8	8	30	100	U.S. EPA, 1980; Horner, 1942; Tainter et al., 1935
2,4-Dinitrophenol	oral	14	Cataracts	3.8	8	30	100	U.S. EPA, 1980; Horner, 1942; Tainter et al., 1935
Diphenylhydrazine	oral	59.8	Increased mortality, decreased growth	2.8	10	28	100	HCI, 1978

TABLE III. SUMMARY OF HAZARD RANKING BASED ON CHRONIC TOXICITY (Continued)

Chemical	Route	Dose ^a (mg/day)	Effect	RV _d ^b	RV _e	Composite ^b Score	RQ	Reference
Ethane, hexachloro-	Inhalation	449	Increased mortality	1.5	10	15	1000	Weeks et al., 1979
Ethane, 1,1,1,2-tetrachloro-							ID	
Ethane, 1,1,2,2-tetrachloro-	Inhalation	22	Fatty liver, elevated ACII in the hypophysis	3.5	5	17	1000	Schmidt et al., 1972
Ethane, 1,1,2-trichloro-							ID	
Ethane, 1,1,2,2-tetrachloro-	Inhalation	7266	Increased mortality due to renal disease	1.0	10	10	1000	Rampy et al., 1978
Ethion							ID	
Ethylbenzene	Inhalation	724	Slight change in kidney and liver weight	1.2	4	4	5000	Wolf et al., 1956
Fluoranthene							ID	
Formaldehyde	Inhalation	12.3	Increased mortality, mucopurulent rhinitis, epithelial dysplasia and squamous metaplasia of nasal cavity	3.9	10	39	100	Swenberg et al., 1980
Hexachlorophene	oral	29.9	Nervousness, paralysis, status spongiosus	3.3	9	30	100	Kimbrough and Gaines, 1971
Hydrogen sulfide							ID	
Indeno(1,2,3-cd)pyrene							ID	
Isoprene	Inhalation	550	Decreased 0/12? consumption (rat), increased number of leukocytes, slightly decreased number of erythrocytes (rabbits), and increase in some organ weights, bronchial vascular lesions and focal liver dystrophy (all)	1.4	4	5	1000	Gostinski, 1965
Lead (metallic)							ID	
Lead (and compounds)	oral	22.4 Pb	Decrease in survival of offspring	3.5	10	35	100	Schroeder and Hittchener, 1971

TABLE III. SUMMARY OF HAZARD RANKING BASED ON CHRONIC TOXICITY (Continued)

Chemical	Route	Dose ^a (mg/day)	Effect	RV _d ^b	RV _e	Composite ^b Score	RQ	Reference
Lead arsenate	oral	598	Decreased survival	1.3	10	13	1000	Fairhill and Miller, 1941
Lead chloride	oral	30.8	Decrease in survival of offspring	3.3	10	33	100	By analogy to lead (and compounds)
Lead fluoroborate	oral	41.2	Decrease in survival of offspring	3.1	10	31	100	By analogy to lead (and compounds)
Lead fluoride	oral	26.5	Decrease in survival of offspring	3.4	10	34	100	By analogy to lead (and compounds)
Lead iodide	oral	49.9	Decrease in survival of offspring	3.0	10	30	100	By analogy to lead (and compounds)
Lead nitrate	oral	37.3	Decrease in survival and longevity	3.1	10	31	100	Schroeder et al., 1965
Lead phosphate	oral	29.3	Decrease in survival of offspring	3.3	10	33	100	By analogy to lead (and compounds)
Lead stearate							10	
Lead subacetate	oral	29.1	Decrease in survival of offspring	3.3	10	33	100	By analogy to lead (and compounds)
Lead sulfate	oral	32.8	Decrease in survival of offspring	3.2	10	32	100	By analogy to lead (and compounds)
Lead sulfide	oral	25.9	Decrease in survival of offspring	3.4	10	34	100	By analogy to lead (and compounds)
Lead thiocyanate	oral	35	Decrease in survival of offspring	3.2	10	32	100	By analogy to lead (and compounds)
Lithium chromate							10	
Mercuric nitrate	Inhalation	1.39	Tremor	5.3	8	42	10	Heal et al., 1937, 1941
Mercuric sulfate							10	
Mercuric thiocyanate							10	
Mercurous nitrate							10	

TABLE III. SUMMARY OF HAZARD RANKING BASED ON CHRONIC TOXICITY (Continued)

Chemical	Route	Dose ^a (mg/day)	Effect	R _{vd} ^b	R _v ^e	Composite ^b Score	R _q	Reference
Mercury, (acetato-0)- phenyl- (phenyl- mercuric acetate)	oral	1.26	Moderate renal damage	5.3	7	37	100	Fitzhugh et al., 1950
Mercury fulminate	-	-	-	-	-	-	10	-
Methyl chloride	Inhalation	221.3	Neuromuscular damage and death	2.0	10	20	1000	Smith and Von Oettingen, 1947a,b
Methyl methacrylate	Inhalation	121.5	Tracheal and suggestive liver histopathologic damage, serum biochemical changes, impaired gastrointestinal motor performance	2.4	7	17	1000	Tansy et al., 1976, 1980a,b
Monochlorobenzene	oral	56	Increased liver and kidney weight	2.9	4	12	1000	Knapp et al., 1971
Monothylamine	-	-	-	-	-	-	10	-
Naphthalene	-	-	-	-	-	-	10	-
Nickel (metallic)	Inhalation	1.79	Pneumonia	5.1	5	26	100	Johansson et al., 1981
Nickel (and compounds)	Inhalation	1.27	Increased mortality, pneumo- coniosis	5.3	10	53	10	Ottolenghi et al., 1974
Nickel ammonium sulfate	oral	22.8	Decreased mortality of offspring	3.5	10	35	100	By analogy to nickel (and compounds) (soluble salt)
Nickel carbonyl	Inhalation	2.7	Increased mortality	4.9	10	49	10	Sunderman et al., 1957
Nickel chloride	oral	10.3	Increased mortality of offspring	4.0	10	40	100	By analogy to nickel (and compounds) (soluble salt)
Nickel (II) cyanide	Inhalation	2.39	Increased mortality, pneumo- coniosis	4.9	10	49	10	By analogy to nickel (and compounds) (nickel sulfide)
Nickel hydroxide	Inhalation	2.0	Increased mortality, pneumo- coniosis	5.0	10	50	10	By analogy to nickel (and compounds) (nickel sulfide)

TABLE III. SUMMARY OF HAZARD RANKING BASED ON CHRONIC TOXICITY (Continued)

Chemical	Route	Dose ^a (mg/day)	Effect	RV _d ^b	RV _e	Composite ^b Score	RQ	Reference
Nickel nitrate	oral	14.5	Increased mortality of offspring	3.8	10	38	100	By analogy to nickel (and compounds) (soluble salt)
Nickel sulfate	oral	12.3	Increased mortality of offspring	3.9	10	39	100	By analogy to nickel (and compounds) (soluble salt)
Nitric acid							10	
p-Nitrophenol							10	
2-Nitrophenol							10	
Nitrophenol (mixed)							10	
Paraldehyde							10	
Pentachloroethane							10	
Phorate							10	
2-Picoline							10	
Plumbane, tetraethyl- (tetraethyl lead)	oral	0.0014	Swollen, friable livers, peripancreatic inflammation, cardiac hypertrophy, slight neuronal damage	9.8	5	49	10	Schepers, 1964
Potassium arsenate	oral	372	Decreased survival; enlargement, fibrosis, and lesions of common bile duct	1.6	10	16	1000	By analogy to sodium arsenate
Potassium arsenite	oral	8.36	Decreased survival	4.1	10	41	10	By analogy to sodium arsenite
Potassium bichromate							10	
Potassium chromate							10	
Pyridine	oral	177	Mortality	2.1	10	21	100	Pollack et al., 1943
Selenious acid	oral	7.33	Decreased body weight, increased mortality	4.2	10	42	10	By analogy to sodium selenite
Selenium (metallic)							10	

TABLE III. SUMMARY OF HAZARD RANKING BASED ON CHRONIC TOXICITY (Cont Inued)

Chemical	Route	Dose ^a (mg/day)	Effect	RV _d ^b	RV _e	Composite ^b Score	RQ	Reference
Selenium (and compounds)	oral	2.59 (selenium)	Increased mortality among neonates	4.9	10	49	10	Schroeder and Mitchener, 1971b
Selenium dioxide (selenium oxide)	oral	6.28	Decreased body weight, increased mortality	4.3	10	43	10	By analogy to sodium selenite
Selenium disulfide							10	
Silver (and compounds)	oral	0.10	Argyria (development of blue/gray skin pigmentation)	7.0	1	7	1000	U.S. DHEW, 1962
Sodium arsenate	oral	385	Decreased survival, enlargement and lesions of bile duct	1.6	10	16	1000	Byron et al., 1967
Sodium arsenite	oral	8.54	Decreased survival	4.1	10	41	10	Schroeder and Balassa, 1967
Sodium bichromate							10	
Sodium bifluoride	oral	13	Mottled teeth resulting from fluoride moiety	3.8	5	19	1000	U.S. EPA, 1980
Sodium chromate							10	
Sodium nitrite	oral	1,409	Marked hepatic atrophy and hemo- siderosis	1.0	7	7	1000	Inal et al., 1979
Sodium selenite	oral	9.8	Decreased body weight, increased mortality	4.0	10	40	100	Schrauzer et al., 1976
Sulfuric acid, thallium (I) salt (thallium sulfate)	oral	0.86	Alopecia, increased kidney weight	5.6	4	22	100	By analogy to thallium I acetate
1,2,4,5-Tetrachloro- benzene	oral	20.5	Elevated alkaline phosphatase and bilirubin levels	3.5	1	3	5000	Braun et al., 1978
2,3,4,6-Tetrachloro- phenol	oral	10.7	Fetotoxicity	4.0	8	32	100	Schwetz et al., 1974a
Tetraethyl pyrophosphate							10	
Thallic oxide [thallium (III) oxide]	oral	1.2	Alopecia, increased kidney weight	5.4	4	22	100	Downs et al., 1960

TABLE III. SUMMARY OF HAZARD RANKING BASED ON CHRONIC TOXICITY (Continued)

Chemical	Route	Dose ^a (mg/day)	Effect	RV _d ^b	RV _e	Composite ^b Score	RQ	Reference
Thallium (metallic)							10	
Thallium (and compounds)	oral	0.70 (thallium)	Alopecia, increased kidney weight	5.7	4	23	100	Downs et al., 1969
Thallium (I) chloride	oral	0.82	Alopecia, increased kidney weight	5.6	4	22	100	By analogy to thallium I acetate
Thallium (I) nitrate	oral	0.91	Alopecia, increased kidney weight	5.6	4	22	100	By analogy to thallium I acetate
Thallium (I) selenide							10	
Toluene	Inhalation	4,036	CNS dysfunction	1.0	7	7	1000	SRC, 1981
Tribromomethane (bromoform)	oral	6.6	Suppression of hepatic phagocytosis	4.3	6	26	100	Hunson et al., 1978
Trichlorfon (trichlorofon)	oral	45	Decreased survival	3.0	10	30	100	Teichmann and Hauschild, 1978
1,2,4-Trichlorobenzene	oral	37.3	Increased adrenal weight	3.1	4	13	1000	Robinson et al., 1981
1,1,1-Trichloroethane	Inhalation	54,592	Histologic changes in hepatocytes	1.0	6	6	1000	McLatt et al., 1975
Trichloroethene	oral	9.5	Decreased immune response	4.0	5	20	1000	Tucker et al., 1980; Sanders et al., 1980
2,4,5-Trichlorophenol	oral	179.6	Mild diuresis; slight degenerative changes in the liver and kidneys	2.1	6	13	1000	McCollister et al., 1961
2,4,6-Trichlorophenol							10	
Triethylamine							10	
Trimethylamine							10	
1,3,5-Trinitrobenzene							10	
Arsenic D004	oral	4.94	Decreased survival	4.5	10	45	10	Schroeder and Balassa, 1967
Cadmium D006	oral	4.49 as Cd	Decreased survival	4.5	10	45	10	Schroeder et al., 1964

TABLE III. SUMMARY OF HAZARD RANKING BASED ON CHRONIC TOXICITY (Continued)

Chemical	Route	Dose ^a (mg/day)	Effect	RV _d ^b	RV _e	Composite ^b Score	RQ	Reference
Chromium (VI) D007	Inhalation	6.4	Epithelial necrosis, atrophy, hyperplasia of the bronchial tree; emphysema-like changes and focal scarring in alveoli of some mice	4.3	8	34	100	Hietesheim et al., 1971
Lead D008	oral	22.4 Pb	Decrease in survival of offspring	3.5	10	35	100	Schroeder and Hitchener, 1971
Selenium D010	oral	2.69 selenium	Increased mortality among neonates	4.9	10	49	10	Schroeder and Hitchener, 1971a
Uranyl acetate	oral	1.68	Kidney injury	5.2	6	31	100	By analogy to uranyl nitrate
Uranyl nitrate	oral	2.1	Degeneration of renal tubular epithelium	5.0	6	30	100	Anghelova, 1966
Vanadium (V) oxide (vanadium pentoxide)	oral	4.277	Mortality	1.0	10	10	1000	Stokinger et al., 1953
Vanadyl sulfate	oral	14	Reduced serum cholesterol and elevated serum fasting glucose levels	3.8	1	3	5000	Schroeder et al., 1970
Vinyl chloride	Inhalation	228	Slight increase in mortality and morbidity	2.0	10	20	1000	Hong et al., 1981
Zinc (metallic)	oral	150	Hypochromic, microcytic anemia	2.2	8	18	1000	By analogy to zinc (and compounds)
Zinc (and compounds)	oral	150 (zinc)	Hypochromic, microcytic anemia	2.2	8	18	1000	Porter et al., 1977; Prasad et al., 1978
Zinc acetate	oral	421	Hypochromic, microcytic anemia	1.6	8	13	1000	By analogy to zinc (and compounds)
Zinc ammonium chloride	oral	558	Hypochromic, microcytic anemia	1.4	8	11	1000	By analogy to zinc (and compounds)
Zinc borate	oral	285	Hypochromic, microcytic anemia	1.8	8	14	1000	By analogy to zinc (and compounds)
Zinc bromide	oral	517	Hypochromic, microcytic anemia	1.4	8	11	1000	By analogy to zinc (and compounds)

TABLE III. SUMMARY OF HAZARD RANKING BASED ON CHRONIC TOXICITY (Continued)

Chemical	Route	Dose ^a (mg/day)	Effect	RV _d ^b	RV _e	Composite ^b Score	RQ	Reference
Zinc carbonate	oral	2,869	Cessation of reproduction, anemia	1.0	9	9	1000	Sutton and Nelson, 1937
Zinc chloride	oral	313	Hypochromic, microcytic anemia	1.8	8	14	1000	By analogy to zinc (and compounds)
Zinc cyanide							10	
Zinc fluoride	oral	12.6	Rotting teeth resulting from fluoride moiety	3.8	5	19	1000	U.S. EPA, 1980a
Zinc formate	oral	357	Hypochromic, microcytic anemia	1.7	8	14	1000	By analogy to zinc (and compounds)
Zinc hydrosulfite							10	
Zinc nitrate	oral	435	Hypochromic, microcytic anemia	1.5	8	12	1000	By analogy to zinc (and compounds)
Zinc phenolsulfonate							10	
Zinc phosphide							10	
Zinc silicofluoride							10	
Zinc sulfate	oral	370	Hypochromic, microcytic anemia	1.6	8	13	1000	Porter et al., 1977; Prasad et al., 1978
Zirconium potassium fluoride							10	

^aEquivalent human dose^bAll values have been rounded to two significant digits.

10 = Insufficient data

IV. REFERENCES

Andersen, E.L., and the Carcinogen Assessment Group of the U.S. Environmental Protection Agency. 1983. Quantitative approaches in use to assess cancer risk. *Risk Analysis* 3(4):277-295.

Dourson, M.L., and J.F. Stara. 1983. Regulatory history and experimental support of uncertainty (safety) factors. *Reg. Toxicol. Pharmacol.* (In press).

Hansch, C., and A.J. Leo. 1981. Pomona College Medicinal Chemistry Project. Seaver Chemistry Laboratory, Claremont, CA.

International Commission on Radiologic Protection (ICRP). 1977. Radionuclide release into the environment: Assessment of doses to man. ICRP Publication 29. Elmsford, NY: Pergamon Press, p. 76.

Kushner, L.M., R.C. Wards, and V. Fong. 1983. The potential use of the ADI in Superfund implementation. Mitre Corporation, McLean, VA. p. 68.

McNamara, B.P. 1976. Concepts in health evaluation of commercial and industrial chemicals. In: *New concepts in safety evaluation: Advances in modern toxicology* 1(1):61-115.

National Institute for Occupational Safety and Health (NIOSH). 1982. Registry of toxic effects of chemical substances. U.S. Department of Health, Education, and Welfare, Cincinnati, OH.

Stara, J.F., D. Kello, and P.R. Durkin. 1980. Human health hazards associated with chemical contamination of aquatic environment. Environ. Health Perspect. 34:145-188.

Stara, J.F., M.L. Dourson, and C.T. DeRosa. 1981. Water quality criteria: methodology and applications. In: Conference Proceedings: Environmental risk assessment: How new regulations will affect the utility industry. Electric Power Research Institute, Palo Alto, CA.

U.S. EPA. 1976 (May 25). Interim procedures and guidelines for health risk and economic impact assessments of suspected carcinogens. Federal Register 41:21402.

U.S. EPA. 1980 (Nov 25). Guidelines and methodology for the preparation of health effects assessment chapters of the ambient water quality criteria documents. Federal Register 45:79347.

U.S. EPA. 1980. Guidelines and methodology used in the preparation of health effects assessment chapters of the consent decree water quality criteria. Federal Register 45:79318-79379.

Weil, C.S., and D.D. McCollister. 1963. Safety evaluation of chemicals. Relationship between short-and long-term feeding studies in designing an effective toxicity test. Agric. Food Chem. 11:486-491.

APPENDIX

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER CLASSIFICATION SYSTEM FOR THE EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO HUMANS*

ASSESSMENT OF EVIDENCE FOR CARCINOGENICITY FROM STUDIES IN HUMANS

Evidence of carcinogenicity from human studies comes from three main sources:

1. Case reports of individual cancer patients who were exposed to the chemical or process.
2. Descriptive epidemiological studies in which the incidence of cancer in human populations was found to vary in space or time with exposure to the agents.
3. Analytical epidemiologic (case-control and cohort) studies in which individual exposure to the chemical or group of chemicals was found to be associated with an increased risk of cancer.

Three criteria must be met before a causal association can be inferred between exposure and cancer in humans:

1. There is no identified bias which could explain the association.
2. The possibility of confounding has been considered and ruled out as explaining the association.
3. The association is unlikely to be due to chance.

In general, although a single study may be indicative of a cause-effect relationship, confidence in inferring a causal association is increased when several independent studies are concordant in showing the association, when

*Adapted from IARC Monographs Supplement 4, Evaluation of the Carcinogenic Risk of Chemicals to Humans, 1982, pp. 11-14.

the association is strong, when there is a dose-response relationship, or when a reduction in exposure is followed by a reduction in the incidence of cancer.

The degrees of evidence for carcinogenicity from studies in humans are categorized as:

1. Sufficient evidence of carcinogenicity, which indicates that there is a causal relationship between the agent and human cancer.

2. Limited evidence of carcinogenicity, which indicates that a causal interpretation is credible, but that alternative explanations, such as chance, bias, or confounding, could not adequately be excluded.

3. Inadequate evidence, which indicates that one of three conditions prevailed: (a) there were few pertinent data; (b) the available studies, while showing evidence of association, did not exclude chance, bias, or confounding; (c) studies were available which do not show evidence of carcinogenicity.

ASSESSMENT OF EVIDENCE FOR CARCINOGENICITY FROM STUDIES IN EXPERIMENTAL ANIMALS

These assessments are classified into four groups:

1. Sufficient evidence of carcinogenicity, which indicates that there is an increased incidence of malignant tumors: (a) in multiple species or strains; (b) in multiple experiments (preferably with different routes of administration or using different dose levels); or (c) to an unusual degree with regard to incidence, site or type of tumor, or age at onset. Additional evidence may be provided by data on dose-response effects, as well as information from short-term tests or on chemical structure.

2. Limited evidence of carcinogenicity, which means that the data suggest a carcinogenic effect but are limited because: (a) the studies involve a single species, strain, or experiment; (b) the experiments are restricted by

inadequate dosage levels, inadequate duration of exposure to the agent, inadequate period of follow-up, poor survival, too few animals, or inadequate reporting; or (c) the neoplasms produced often occur spontaneously and, in the past, have been difficult to classify as malignant by histological criteria alone (e.g., lung and liver tumors in mice).

3. Inadequate evidence, which indicates that because of major qualitative or quantitative limitations, the studies cannot be interpreted as showing either the presence or absence of a carcinogenic effect; or that within the limits of the tests used, the chemical is not carcinogenic. The number of negative studies is small, since, in general, studies that show no effect are less likely to be published than those suggesting carcinogenicity.

4. No data, indicating that data were not available to the Working Group.

The categories "sufficient evidence" and "limited evidence" refer only to the strength of the experimental evidence that these chemicals are carcinogenic, and not to the extent of their carcinogenic activity nor to the mechanism involved. The classification of any chemical may change as new information becomes available.

EVALUATION OF CARCINOGENIC RISK TO HUMANS

At present, no objective criteria exist to interpret data from studies in experimental animals or from short-term tests directly in terms of human risk. Thus, in the absence of sufficient evidence from human studies, evaluation of the carcinogenic risk to humans was based on consideration of both the epidemiologic and the experimental evidence. The breadth of the categories of evidence defined above allows substantial variation within each category. The decisions reached by the Working Group regarding overall risk incorporated these differences, even though the differences could not always be reflected adequately in

the placement of an exposure into a particular category.

The chemicals, groups of chemicals, industrial processes, or occupational exposures were thus put into one of three groups:

Group 1

The chemical, group of chemicals, industrial process, or occupational exposure is carcinogenic to humans. This category was used only when there was sufficient evidence from epidemiologic studies to support a causal association between the exposure and cancer.

Group 2

The chemical, group of chemicals, industrial process, or occupational exposure is probably carcinogenic to humans. This category includes exposures for which, at one extreme, the evidence of human carcinogenicity is almost "sufficient," as well as exposures for which, at the other extreme, it is inadequate. To reflect this range, the category was divided into higher (Group A) and lower (Group B) degrees of evidence. Usually, category 2A was reserved for exposures for which there was at least limited evidence of carcinogenicity to humans. The data from studies in experimental animals played an important role in assigning studies to category 2, and particularly those in Group B; thus, the combination of sufficient evidence in animals and inadequate data in humans usually resulted in a classification of 2B.

In some cases, the Working Group considered that the known chemical properties of a compound and the results from short-term tests allowed its transfer from Group 3 to 2B or from Group 2B to 2A.

Group 3

The chemical, group of chemicals, industrial process, or occupational exposure cannot be classified as to its carcinogenicity to humans.